REMARKS

Reconsideration of this application is respectfully requested.

Claims 283-362, 364-380, 382-398, 400-404 and 406-460 were previously pending in this application. Claims 300, 315 321, 328, 347, 364-365, 376-377, 382-383, 394-395, 400-401, 406-407, 439 and 442 have been amended. Claims 461-463 have been added and claim 440 has been canceled. Accordingly, claims 283-362, 364-380, 382-398, 400-404, 406-439 and 441-463 are presented for further examination on the merits.

In a sincere effort to define their invention more clearly, Applicants have amended the claims as follows. **First**, claim 300 has been amended to recite as a Markush member therein "a nucleotide analog-containing nucleic acid polymer." Similarly, claims 315, 321 and 328 have each been amended to recite also as a Markush member "a nucleotide analog-containing oligo- or polynucleotide." By amending the four claims thusly, Applicants have clarified the analog in two ways. The analog is defined as a nucleotide analog and the nucleotide analog is incorporated or associated with a nucleic acid polymer or an oligo- or polynucleotide.

Second, claim 347 has been amended and now recites "wherein said signal generating portion or said one or more chemically modified or artificially altered polynucleotides are capable of being detected by means of a measurement selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a phosphorescent measurement, a chemiluminescent measurement, a colorimetric measurement, a microscopic measurement, an electron density measurement, and a radioactive measurement. The reference to "a binding step on an insoluble phase" has been deleted as a Markush member in claim 347 and is now present in new claim 461. That new claim recites that the signal generating portion or the chemically modified or artificially altered polynucleotides are capable of being detected by a binding member in an insoluble phase. It is noted that the binding member in an insoluble phase language was present in the originally filed claims in the priority document, U.S. Patent Application Serial No. 06/491,929, filed on May 5, 1983. See, for example, claims 52, 65 and 143.

Third, the dependencies in four sets of claims (364-365, 382-383, 400-401 and 406-407) have been changed, again in an effort to clarify the subject matter

being claimed. As now amended, claims 364 and 365 depend from claims 443, 445 or 447. Claims 382 and 383 depend from 449, 451 or 453. Claims 400 and 401 now depend from claims 455, 457 or 458. Finally, claims 406 and 407 each depend from claim 459.

Fourth, claim 439 has been amended to depend from claims 442, 443, 445, 447, 449, 451, 453, 455, 457, 458 or 459. In addition, claim 439 recites that the step of detecting the analyte . . . "comprises carrying out a binding step on an insoluble phase." Because claim 439 is directed to a process for detecting an analyte, the reference to a "binding step on an insoluble phase" is altogether clear and proper. As the Examiner astutely observed, claims 439 and 440 both depended from a canceled claim (363). Claim 440 has been canceled.

Fifth, claim 442 has been changed to depend from new claim 462. Previously this claim depended from claim 441 that ultimately depended from any of claims 283-294. New claim 462 recites the composition of any of claims 283, 284, 286, 287, 288, 289, 291, 292, 293 or 294" - none of which claims recite a complex or its formation.

Sixth, each of claims 376, 377, 394 and 395 has been amended to recite that "fixing or immobilizing the analyte takes place before forming the complex in said complex forming step" (in the case of claims 376 and 394) or "after forming the complex in said complex forming step" (in the case of claims 377 and 395). The insertion of the phrase "in said complex forming step" is believed to meet the Examiner's query regarding which complex is meant.

Lastly, new claim 463 has been added commensurate with Applicants' complete and broad disclosure. This claim recites "[t]he composition according to any of claims 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293 or 294, wherein said molecular bridging entity comprises a polymer selected from the group consisting of a nucleic acid-protein polymer, a nucleic acid-polypeptide polymer, a nucleic acid-polysaccharide polymer and a polypeptide-polysaccharide polymer, said polymer comprising one or more chemically modified purines, one or more chemically modified pyrimidines, one or more chemically modified sugar moieties, or one or more chemically modified phosphate moieties, or a combination of any of the foregoing." Support for new claim 463 is found variously as set forth below.

For the terms "nucleic acid-protein polymer" and "nucleic acid-polypeptide polymer" in new claim 463, this language is found in the instant disclosure, including page 23, second paragraph, through page 24, first paragraph; and Examples 15 and 19-20. Support is also found at page 110, second paragraph, in U.S. Patent Application Serial No. 06/391,440, filed on June 23, 1982. The contents of the foregoing application are incorporated into the present application by virtue of the statements found in the first paragraph on page 21 in the instant specification. Applicants note that two divisional applications have been issued from Serial No. 06/391,440, including U.S. Patents Nos. 5,241,060 and 5,260,433, issued on August 31, 1993 and November 9, 1993, respectively. The disclosure from page 110 of Serial No. 06/391,440 is also found in the '060 Patent at column 30, line 59, through column 31, line 12; and in the '433 Patent at column 30, line 59, through column 31, line 13. Attention is also drawn to the originally filed claims in Serial No. 06/391,440, including claims 55-60, 98-100, 139-140 and 168.

For the recitation "nucleic acid-polysaccharide polymer" in new claim 463, this language is supported by the original disclosure, including page 25, first full paragraph; and Examples 18-19. Support is also found in Serial No. 06/391,440 and the two aforementioned '060 and '433 Patents. In Serial No. 06/391,440, the supporting disclosure is found on page 97, lines 13-17; page 99, last paragraph, through page 100, first paragraph; and originally filed claims 23, 62-64, 91, 113, 115-118, 150, 191 and 193-196. For "polypeptide-polysaccharide," this language is drawn from the originally filed claims in Serial No. 06/391,440, including claim 199. With respect to "chemically modified purines," "chemically modified pyrimidines," chemically modified sugar moieties," and "chemically modified phosphate moieties," it is believed that no issue of new matter is presented by any of these recitations in new claim 463. All of the foregoing language is supported by the original disclosure, or by the disclosures of issued U.S. patents whose contents have been incorporated by reference into the present application. Entry of new claim 463 is respectfully urged.

It is believed that none of the foregoing amendments to the claims or the new claims inserts new matter into the disclosure. All of the amendments, including the new claims have been made in response to rejections at hand. Thus, the amendments serve to meet the Examiner's rejections or to adopt his suggestions.

Applicants and their attorney sincerely appreciate the indication from the Examiner that some rejections and/or objections have been withdrawn, including the rejection under 35 U.S.C. §103(a) as well as the basis for various rejections and/or objections. Acknowledgment with appreciation is also made of the Examiner's comments on page 8 that a number of claims were objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form with all the limitations of the base claim and any intervening claims. It is believed, however, that with the implementation of the above amendments to the claims and consideration of the remarks and evidence directed to the anticipation rejection (35 U.S.C. §102(a)), the present application will have been placed in an allowable condition.

Acknowledgement is made of the Examiner's comments that the foreign patent application prosecution was incomplete. Based upon a brief telephone conversation with Examiner Marschel subsequent to the issuance of the instant Office Action, Applicants' attorney understands that no further action is required with respect to such foreign patent applications.

Before addressing the issues in the October 27, 1998 Office Action, Applicants would like to bring attention to the U.S. Patent Office and the Examiner yet another issued patent that is covered by the present invention. This patent - the *fourth* such patent to be issued to another party that is covered by the present invention - was issued on July 10, 1991 by the European Patent Office as EP 0 204 510 B1 to Amoco Corporation. EP 0 204 510 B1 was based upon a priority document, U.S. Patent Application Serial No. 739,937, filed on May 31, 1985 in the name of Mark Leo Collins as the sole inventor. Relying upon the results of a recent computer search, Applicants do not believe that the Amoco '937 application (or any related continuation) has been issued as a patent by the U.S. Patent Office. In any case, Applicants point out that Amoco's priority document was filed more than two years after the May 5, 1983 filing date of their own priority document (U.S. Patent Application Serial No. 06/491,929). Applicants further point out that Amoco's priority document was also filed six months after the predecessor assignee offered its BioBridge® product for sale in product literature dated November 1984. And beyond that, Amoco's priority document was also filed more than five months after the December 19, 1984 publication date of Applicants' corresponding European patent application (EP 0 128 332 A1). A copy of Amoco's EP 0 204 510 B1 is attached to this Amendment as Exhibit A.

The Objection and Rejection Under 35 U.S.C. §112, First Paragraph

The specification stands objected to and claims 315, 321, and 328 were rejected under U.S.C. §112, first paragraph, for not providing support for the invention as is now claimed. In the Office Action (pages 2-3), the Examiner stated:

> The NEW MATTER rejection directed to the phrase in claim 300, lines 3-4, the phrase being "an analog-containing polymer" is reiterated and maintained as given in the previous office action, mailed 3/11/97. This phrase adds NEW MATTER in that written basis for generic polymers containing analogs has not been found. Consideration of the support cited by applicants reveals that polynucleotides of various types are listed but not more generic polymers. Another interpretation is that NEW MATTER is added via unclarity of the metes and bounds of such polymers. Claims 315, 321, and 328 also contain this NEW MATTER and claims 317 and 318 via dependence from the above claims. Applicants argue that several polymer types are cited such as polysaccharides and proteins as well as nucleic acid polymers. This is non-persuasive since consideration of claims 315 etc. reveals that they are firstly limited to oligo- or polynucleotides. Therefore, protein polymers, for example, are not related to the analog limitations of claims 315 etc. It is noted that attachments to oligo- or polynucleotides have written support as filed but not the generic concept of analogs as given in claims 315 etc. Amendment to such attachments to replace the analog amendments to these claims is suggested.

The objection and rejection for new matter are respectfully traversed.

As indicated in the opening remarks above, Applicants have amended each of claims 300, 315, 321 and 328 to recite "a nucleotide analog-containing nucleic acid polymer" (claim 300) or a nucleotide analog-containing oligo- or polynucleotide (claims 315, 321 and 328).

In view of the above amendments to the rejected claims, it is respectfully requested that the objection and rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 347, 364, 365, 376, 377, 382, 383, 394, 395, 400, 401, 406, 407, 439, 440, 442, 444, 446, 448, 450, 452, 454, 456, and 460 stand rejected for indefiniteness under 35 U.S.C. § 112, second paragraph. In the Office Action (pages 3-5), the Examiner stated:

> [1] The last line of claim 347 is confusing in context in citing a binding step in a selection group of a composition claim.
>
> [2] Claims 364 and 365 are vague and indefinite because complex formation cited therein conflicts with claims from which they depend. For example, claim 364 depends from claim 444 wherein claim 444 cites the providing of a complex, cited in line 3 therein, between a molecular bridging entity and the one or more signalling entities and a separate step wherein said complex forms a further complex with the analyte. This conflicts with claim 364 wherein the analyte first complexes with the bridging entity and thereafter a second complex is formed by the addition of the signalling entity. Similarly, claims 446 and 448 conflict with claim 364. Similarly, claim 365 seems to repeat the complex ordering in the same manner as claims 444, 446, or 448. What added limitation(s) are therefore meant by the wording of claim 365 over claims 444, 446, or 448? The same set of conflicts exist between claims 382 and 383 versus claims 450, 452, and 454; as well as claims 400 and 401 versus claim 456; as well as claims 406 and 407 versus claim 460
>
> [3] Claims 439 and 440 are vague and indefinite due to depending from a canceled claim.
>
> [4] Claim 442 is vague and indefinite because claim 442 cites the formation of a complex that is apparently already formed in claims 285, 290, and 294. What is meant by this repetitive citation of complex formation? Clarification is requested.
>
> [5] Claims 376, 377, 394, and 395 are vague and indefinite because certain claim dependencies result in two complexes being formed. These claims cite fixing or immobilizing before forming the complex, but it is unclear which complex is meant.

The indefiniteness rejection is respectfully traversed.

In order to ensure that each and every matter raised in the indefiniteness rejection has been thoroughly addressed, Applicants have inserted bold bracketed numbers above. The remarks below follow the matters designated in those numbered bold brackets.

[1] As indicated in the opening remarks above, claim 347 has been amended by deleting subject matter directed to "a binding step on an insoluble phase." By so doing, the remaining Markush members in claim 347 all refer to

types of measurement the means of which detection can be carried out. Furthermore, new claim 461 recites that the signal generating portion or the chemically modified or artificially altered polynucleotides are "capable of being detected by a binding member in an insoluble phase." It is believed that both changes - the deletion of the "binding step on an insoluble phase" in claim 347 and its recitation in new claim 461 - serve to clarify Applicants' invention and reduce if not eliminate any confusion regarding a binding step in association with a composition.

[2] In view of the amendments to claims 364, 365, 382, 383, 400, 401, 406 and 407, as discussed in the opening remarks above, it is believed that any conflict to other complexes in other claims from which these claims depend, has been removed.

[3] With the amendments to claim 439 and the cancellation of claim 440, the issue of claims depending from canceled claims has been obviated.

[4] As discussed in the opening remarks above, claim 442 now depends from new claim 462, the latter depending from claims 283, 284, 286, 287, 288, 289, 291, 292, 293 or 294. None of those claims refers to a complex. Thus, claim 442 is believed to be clear and definite with respect to the second step of "forming a complex comprising said composition and said analyte."

[5] As noted above, claims 376, 377, 394 and 395 have been amended. As amended, claims 376 and 394 recite "fixing or immobilizing the analyte takes place before forming the complex in said complex forming step." As amended, claims 377 and 395 recite "fixing or immobilizing the analyte takes place after forming the complex in said complex forming step." The insertion of the phrase "in said complex forming step" is believed to have clarified which complex is meant in each of claims 376, 377, 394 and 395.

In view of the above amendments to the claims and the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

The Rejection Under 35 U.S.C. §102

Claims 283-296, 298-301, 304, 307, 309-321, 323-333, 335-340, 347, 350, 353, 358-362, 364, 366, 367, 374-376, 378-380, 382, 384, 385, 392-394, 396-398, 400, 402, 403, 406, 408, 409, 411, 413, 414, 416, 418, 419, 422-425, 432, 433, 436-438, 441-443, 445, 447, 449-455, and 457-459 stand rejected under 35 U.S.C. § 102 (b) for anticipation by Dunn et al. ["A Novel Method to Map Transcripts: Evidence for Homology between an Adenovirus mRNA and Discrete Multiple Regions of the Viral Genome," Cell 12:23-36 (1977)]. In the Office Action (pages 5-8), the Examiner stated:

> Dunn et al. reads on the above listed claims due to its disclosure of an immobilized target analyte wherein a bridging entity is hybridized thereto followed by washing and then the hybridization of a nick translated radiolabelled signalling entity that is made up of a heterogeneous mixture of radiolabelled fragments produced as a result of the nick translation process. This nick translation process also results in a ratio of signalling entities as being clearly greater than 1 as compared to bridging entities, but is unclear how much greater than 1. This rejection is maintained and reiterated as given in the previous office action, mailed 3/11/97. Applicants firstly argue that the Dunn et al. disclosure utilizes sandwich hybridization wherein the two reagent entities hybridize to two separate portions of the target. This is entirely contrary to the Dunn et al. reagents wherein there is an entity that hybridizes to the target RNA said entity having a tail. The nick translated signal entities hybridize to said tail and not to the target RNA thus making this argument of applicants moot as directed to a mischaracterization of the disclosure of Dunn et al. The second argument is that the signalling entities be substantially incapable of hybridizing to the molecularly recognizable portion on the analyte. This argument is also non-persuasive because the Dunn et al. disclosure labels the target only via a sandwich formed wherein one reagent hybridizes to the target thus making it an incapability for the signalling entity to hybridize thereto thus inherently meeting the instant claim limitations. Another element of support for the substantial incapability of the signalling entity to hybridize to the target recognizable portion is that these are distinct sequences in that one is Adenovirus type 2 sequence and the other is SV40 sequence, These are well known to be different and distinct sequences thus being substantially incapable of hybridization as required for the instant claims and also supporting the rejection. Applicants then argue a lack of one continuous chain comprising the complementary sequences for the molecular bridging sequence entity and the sequence for the signalling entity. This is confusing and non-persuasive since this is exactly what is both disclosed in Dunn et al. and in the instant claims. Again mischaracterization of the instant invention and/or the disclosure of Dunn et al. is not persuasive to overcome the rejection. Applicants then summarize several references that refer to sandwich hybridization and credit various authors for

> suggesting or disclosing them. It is acknowledged that sandwich hybridization is a phrase that may be applied to both the Ranki et al. type of assay as well as the Dunn et al. type of assay but that the location of the entity that is the target is different but that there are similarities in the sandwiches that are formed. Since the Dunn et al. disclosure is directed to mapping RNA sequences, this is deemed to be the target. This target is located the same both in the Dunn et al. disclosure as well as in the practice of the instant invention and thus supports this rejection. It is noted that the target in the Ranki et al. type of sandwich hybridization is in the middle of the sandwich and different from that of Dunn et al. as well as the instant invention. Applicants then argue that Dunn et al. did not teach the detection of an unknown analyte. This is non-persuasive because the analyte must be known regarding sequence in both the Dunn et al. disclosure as well as the instant invention in order to direct the synthesis of the target recognition portion of the bridging entity. This was required for the Dunn et al. procedure as well as for the instant invention. The bridging entity, in other words, must be designed from knowledge of the target sequence.
>
> The anticipation rejection is respectfully traversed.

In response, Applicants are submitting herewith as Exhibit B the Declaration of James G. Wetmur who is both a Professor of Microbiology and Human Genetics and Professor of Microbiology at Mount Sinai School of Medicine in New York City. Dr. Wetmur is a highly respected scientist whose professional career in the field of nucleic acid technology spans more than three decades and includes extensive investigations into nucleic acid hybridization reactions and DNA renaturation kinetics. A copy of Dr. Wetmur's curriculum vitae (CV) is attached as the first exhibit to his Declaration. During the course of his professional career and scientific investigations that have resulted in more than eighty publications, Dr. Wetmur has examined nucleic acids including DNA from a number of different species using a number of different and diverse formats. As indicated in his Declaration, Dr. Wetmur is thoroughly familiar with nucleic acid detection formats and nucleic acid probe technology, having spent the better part of his professional career exploring their use as investigative tools for nucleic acid hybridization and kinetic studies. It is respectfully submitted that Dr. Wetmur's knowledge and experience qualifies him as a person of ordinary skill in the art to which the present invention pertains.

As also indicated in his Declaration, Dr. Wetmur read the specification and reviewed the pending claims in this application. He also read the two most recent Office Actions dated March 11, 1997 and October 27, 1997, respectively, as well as Applicants' July 25, 1997 Amendment Under 37 C.F.R. §1.115 filed in

response to the former. Dr. Wetmur, who is an Enzo consultant and was compensated for his services in connection with his Declaration, is also familiar with the document cited against the pending claims, Dunn and Hassell ["A Novel Method to Map Transcripts: Evidence for Homology between an Adenovirus mRNA and Discrete Multiple Regions of the Viral Genome," Cell 12:23-36 (1977)]. Dunn's 1977 publication, the Examiner's remarks on the anticipation rejection, and the pending claims in this application are attached to Dr. Wetmur's Declaration as Exhibits 2-4, respectively.

In Paragraph 6 in his Declaration, Dr. Wetmur describes the sandwich hybridization technique first disclosed by Dunn and Hassell (1977). He points out that sandwich hybridization requires the use of two nucleic acid probes, one an immobilized capture probe and the other a radioactively labeled signaling probe. In sandwich hybridization, the capture probe and the signaling probe are complementary to adjacent nonoverlapping sequences in the target nucleic acid. As noted by Dr. Wetmur, the capture probe and the signaling probe in sandwich hybridization and in Dunn's own cited disclosure meet the classical and art-accepted definitions and descriptions of a nucleic acid probe. Dr. Wetmur notes that a nucleic acid probe of known sequence interacts with a corresponding target nucleic acid for the purpose of determining its presence. Dr. Wetmur points out in his Declaration that the interaction of a nucleic acid probe with its yet to be identified target analyte is a familiar and well-recognized scientific concept that has existed for many years. In support of the latter statement, Dr. Wetmur provides a summary of descriptions and definitions for probes and target analytes taken from several leading textbooks and scientific dictionaries. These descriptions and definitions for probes including nucleic acid probes and target analytes are set forth in subparagraphs A, B, C(i), C(ii) and D following Paragraph 6, and are included as Exhibits 5-9 to Dr. Wetmur's Declaration.

Later in Paragraph 7, Dr. Wetmur points out that the sandwich hybridization technique was directed toward overcoming the problem of non-specific binding of non-analyte sequences to capture sequences. According to Dr. Wetmur, non-specific binding had limited the specificity of analyte detection. By using a signaling sequence complementary to a portion of the nucleic acid analyte, an additional level of specificity was introduced by the sandwich hybridization technique. That is to say, the signaling sequence hybridized to the bound nucleic acid sequence in preference to non-specifically bound non-analyte sequences.

In subparagraph (A) following Paragraph 7, Dr. Wetmur explains that the RNA target analyte in Dunn and Hassell (1977) comprised both adenovirus RNA containing SV40 sequences and adenovirus RNA lacking SV40 sequences as well as cellular messenger RNAs also lacking SV40 sequences. He further explains that each of the capture sequences immobilized on their filter was capable of binding specifically to a subset of both types of adenovirus RNA and non-specifically to the remaining adenoviral and cellular RNAs. According to Dr. Wetmur, only adenovirus RNAs that also contained SV40 sequences were able to hybridize to the signaling sequence, specifically identifying these particular messages that were of interest to Dunn and Hassell.

Dr. Wetmur declares in the next subparagraph (B) that the present invention does not fulfill the accepted criteria for "sandwich hybridization" because it does not increase the specificity of analyte detection by providing two analyte-specific probes as in the case of Dunn and Hassell (1977). Dr. Wetmur goes on to explain that among other objects and features, the present invention discloses unique means and compositions for extending the range of applicability of expensive-to-produce signaling sequences wherein the signaling moiety is attached to an arbitrary nucleic acid sequence not found in the analyte of interest. The specificity for linking any signaling sequence to any particular analyte is mediated through a linker nucleic acid sequence containing one portion complementary to the analyte nucleic acid and a second portion complementary to the arbitrary nucleic acid sequence placed in the signaling molecule.

In subparagraph (C), Dr. Wetmur describes in further detail that in sandwich hybridization, including its first disclosure in Dunn and Hassell (1977), two nucleic acid probes - one a capture probe and the other a signaling probe - were used to map target analytes in the form of viral RNA transcripts. Dunn's capture probe was adenovirus type 2 DNA immobilized to a nitrocellulose filter and their signaling probe was ^{32}P-labeled SV40 DNA. Dr. Wetmur explains that both of Dunn's probes - the capture probe and the signaling probe - were complementary to different portions of the target RNA transcript analyte being mapped. According to Dr. Wetmur, the foregoing characterization is confirmed by Dunn and Hassell's own description in their 1977 paper (page 23, right column):

> An outline of the procedure we have used to map viral RNAs comprised of both SV40 and Ad2 sequences is shown in Figure 1B. Ad2 DNA is cleaved with a restriction endonuclease, the resulting fragments separated by agarose gel electrophoresis and transferred to

> a nitrocellulose filter (Southern, 1975). **Unlabeled RNA [analyte] extracted from cells** lytically infected with an adenovirus-SV40 hybrid is hybridized to the immobilized DNA fragments, the filters are washed to remove unannealed RNA and hybridization is continued with SV40 DNA that has been labeled in vitro with ^{32}P to high specific activity (citations omitted). After again washing the filters, the Ad2 DNA fragments complementary to RNA which contains SV40 sequences can be identified by autoradiography. We have in this way **demonstrated the existence of an RNA molecule consisting of Ad2 and SV40 sequences in one continuous chain** and have mapped the location of the sequences which serve as template for its synthesis on the Ad2 + ND1 genome. [bold, underline & parenthetical added]

As set forth in Paragraph 8 of his Declaration, it is Dr. Wetmur's conclusion that that the target analyte in Dunn and Hassell (1970) was and could only have been the RNA transcripts that the authors were seeking to map. Dr. Wetmur reached this conclusion because the authors had prepared their capture probe by isolating the adenovirus type 2 DNA and immobilizing it onto a nitrocellulose filter, and they had prepared their signaling probe by labeling SV40 DNA with hot phosphorus (^{32}P). Therefore, the target analyte in Dunn and Hassell (1977) had to be the only remaining entity in their disclosure, namely, the RNA transcript that became sandwiched between the immobilized capture probe and the signaling probe. Dr. Wetmur points out that this is the only characterization that fits the sandwich hybridization technique as disclosed by Dunn and Hassell (1977) and as later described in the scientific literature. In addition to that portion from Dunn and Hassell (1977) [page 23, right column] quoted in subparagraph 7(C), Dr. Wetmur's conclusion regarding the RNA transcript being the analyte in their disclosure is also supported by Dunn's own Figure 1B on page 24, specifically, the lower right portion. According to Dr. Wetmur, in that illustration of their sandwich hybridization technique, Dunn and Hassell clearly depict the target RNA transcript analyte as being sandwiched between the capture probe (immobilized Ad2 DNA) and the signaling probe (SV40 ^{32}P-labeled DNA).

Dr. Wetmur's conclusion that Dunn's analyte was the RNA transcript is also based on the fact that the authors were mapping RNA transcripts. In Paragraph 9 of his Declaration, Dr. Wetmur points out that this is acknowledged even by the Examiner in the October 27, 1997 Office Action (page 7, lines 16-17) where he states: "since the Dunn et al. disclosure is directed to mapping RNA sequences, this is deemed to be the target." Dr. Wetmur also points to several portions in Dunn and Hassell (1977) as support for RNA transcript mapping, including the very title of Dunn's article.

Dr. Wetmur writes in Paragraph 10 that he finds it of some significance that Dunn and Hassell (1977) were the first to describe the sandwich hybridization technique and that the literature generally accords them recognition for having done so. In support of his conclusion that Dunn's target analyte was the RNA transcript sandwiched between their immobilized capture probe and their isotopically labeled signaling probe, Dr. Wetmur points to no less than eleven separate publications, including textbooks, scientific articles and reviews and a scientific dictionary. These eleven publications are described in subparagraphs A through I following Paragraph 10. Pages taken from the eleven publications have been attached to Dr. Wetmur's Declaration as Exhibits 10 through 18.

In Paragraph 11 of his Declaration, Dr. Wetmur points out that among the literature even Dunn's own group and coauthors support his conclusion that the RNA transcripts in Dunn and Hassell (1977) were the target analyte. Two subsequent Dunn publications, one in 1978 and the other in 1980, are described in subparagraphs A and B following Paragraph 11 in Dr. Wetmur's Declaration. Exhibits 19 and 20 of his Declaration include pages copied from Dunn's 1978 and 1980 publications, respectively.

Dr. Wetmur states in Paragraph 12 his opinion and conclusion that the present invention and its elements represented by the pending claims in this application are different in at least two material elements from any composition or method disclosed in Dunn and Hassell (1977). In subparagraph A following Paragraph 12, Dr. Wetmur notes that the first material claim element lacking in Dunn and Hassell (1977) is the presently claimed signaling entities that are capable of binding to or hybridizing with one or more molecular bridging entities which are distinct from the target analyte. As explained by Dr. Wetmur, in sandwich hybridization as disclosed in Dunn and Hassell (1977), both the capture probe (immobilized adenovirus type 2 DNA) and the the signaling probe (^{32}P-labeled SV40 DNA) are complementary to the target RNA transcript analyte. Thus, Dunn's capture and signaling probes in the sandwich hybridization technique hybridize to different portions of the target RNA transcript analyte. Dr. Wetmur explains that in contrast to Dunn's disclosure, the present invention specifically recites in the pending claims a requirement that the molecular bridging entity and the signaling entity be capable of binding to or hybridizing with each other through their respective nucleic acid portions. Thus, according to Dr. Wetmur, the present invention including the claimed compositions is materially different from any disclosed or used in Dunn and Hassell (1977).

According to Dr. Wetmur in subparagraph B (following Paragraph 12), a second material element missing altogether in Dunn and Hassell (1977) is the requirement in the present claims that the signaling entity or entities be substantially incapable of binding to or hybridizing with the analyte. It is Dr. Wetmur's opinion and conclusion that this limitation in the claims in and of itself materially distinguishes the present invention from the sandwich hybridization technique disclosed in Dunn and Hassell (1977). As explained by Dr. Wetmur, what is disclosed in Dunn's paper is a sandwich hybridization technique that involves mapping target RNA transcript analytes. In the sandwich hybridization technique employed by Dunn and Hassell (1977), the target analyte (viral RNA transcripts) is sandwiched between the capture probe (immobilized adenovirus DNA type 2), and the signaling probe (radioactively labeled ^{32}P fragment of SV40 DNA). The signaling probe hybridizes to SV40 sequences found in Dunn's target RNA transcript analyte - and those SV40 sequences are not present in Dunn's capture probe. According to Dr. Wetmur, because the signaling entities are incapable of interacting with the analyte, the present invention eschews sandwich hybridization altogether. Dr. Wetmur notes that this difference makes the present invention and claimed compositions materially different from Dunn and Hassell (1977).

Dr. Wetmur follows in Paragraph 13 with his opinion and conclusion that several of the Examiner's assertions in the latest anticipation rejection set forth in the October 27, 1997 Office Action, including his characterization of Dunn and Hassell (1977) and the sandwich hybridization technique, are incorrect. Dr. Wetmur respectfully submits that certain erroneous references to what is the analyte in Dunn and Hassell (1977) are inconsistent and run altogether contrary to the authors' own disclosures and the scientific literature.

In subparagraph A following Paragraph 13, Dr. Wetmur notes that as set forth in Paragraphs 10A, 10B and 10D of his Declaration, Dunn and Hassell (1977) were probably the first to disclose the use of the sandwich hybridization technique which in their disclosure was confined to isotopic labelling. Dr. Wetmur points out that for the two decades since Dunn's disclosure, the scientific literature has consistently described sandwich hybridization as requiring and employing two nucleic acid probes - an immobilized capture probe and a signaling probe. As noted by Dr. Wetmur, the two probes hybridize to two separate and distinct portions of the target nucleic acid analyte (which in the case of Dunn and Hassell (1977) is the target RNA transcript analyte). Dunn's signaling probe hybridized to sequences in

the target RNA transcript analyte, that target analyte being sandwiched between the immobilized capture probe and the signaling probe.

In subparagrpah A(i), Dr. Wetmur respectfully submits that it was an error when the Examiner stated in the October 27, 1997 Office Action:

> Applicants firstly argue that the Dunn et al. disclosure utilizes sandwich hybridization wherein the two reagents entities hybridize to two separate portions of the target. **[1]**This is entirely contrary to the Dunn et al. reagents wherein there is an entity that hybridizes to the target RNA said entity having a tail. **[2]**The nick translated signal entities hybridize to said tail and not to the target RNA thus making this argument of applicants moot as directed to a mischaracterization of the disclosure of Dunn et al. [parenthetical numbers added]

With respect to the assertions designated **[1]** and **[2]**, Dr. Wetmur points out in subparagraph A(ii) that Dunn and Hassell (1977) specifically disclose in their opening Summary (page 23) the following series of events in their sandwich hybridization technique:

> RNA extracted from cells infected with an adenovirus-SV40 hybrid (Ad2+ND1) **[target analyte]** was hybridized to restriction endonuclease fragments of adenovirus type 2 (Ad2) DNA immobilized on nitrocellulose filters **[capture probe]**. RNA containing both Ad2 and SV40 sequences formed duplexes through their Ad2 sequences leaving their SV40 sequences as protruding tails.
>
> Annealing with ^{32}P-labeled SV40 DNA **[signaling probe]** caused these tails **[of the target analyte]** to become labeled . . ."
> [bold parentheticals added].

In Dunn's cited disclosure, according to Dr. Wetmur, it was their radioactively labeled signaling probe that hybridized to an SV40 tail sequence present in their ***target RNA transcript analyte***. Dr. Wetmur points out that Dunn's immobilized capture probe clearly contained no such tail sequence. Furthermore, Dr. Wetmur notes that to assert that in Dunn and Hassell (1977) there is an "entity that hybridizes to the target RNA said entity having a tail," would require one to accept wrongly that Dunn's analyte was the immobilized capture probe. It is Dr. Wetmur's opinion that such a wrong acceptance would refute Dunn's own disclosure as well as two decades of scientific explanations of sandwich hybridization, including the cited authors' subsequent publications on the subject. Moreover, in Dr. Wetmur's opinion, that acceptance would require one to discard the very clear and fundamental distinction that has been recognized and accepted over the years

between a probe and its target analyte.

In subparagraph B, Dr. Wetmur notes that as explained above in Paragraphs 7, 12B and 13A(ii) of his Declaration, Dunn's ^{32}P-labeled SV40 DNA signaling probe hybridized only to the target RNA transcript analyte. Dr. Wetmur explains that the pending claims require that the signaling entity or entities be substantially incapable of binding to or hybridizing with the analyte. Thus, Dr. Wetmur believes that the following statements by the Examiner were in error:

> The second argument is that the signalling entities be substantially incapable of hybridizing to the molecularly recognizable portion on the analyte. **[1]**This argument is also non-persuasive because the Dunn et al. disclosure labels the target only via a sandwich formed when one reagent hybridizes to the target thus making it an incapability for the signalling entity to hybridize thereto thus inherently meeting the instant claim limitations.
>
> **[2]**Another element of support for the substantial incapability of the signalling entity to hybridize to the target recognizable portion is that these are distinct sequences in that one is Adenovirus type 2 sequence and the other is SV40 sequence. **[3]**These are well known to be different and distinct sequences thus being substantially incapable of hybridization as required for the instant claims and also supporting the rejection. [bold parenthetical added]

With respect to **[1]**, Dr. Wetmur respectfully submits in subparagraph B(i) that this assertion is incorrect because Dunn's signaling probe (^{32}P-labeled SV40 DNA) is clearly disclosed as hybridizing to their target RNA transcript analyte through the protruding SV40 tail sequences present in the target analyte. This, according to Dr. Wetmur, has already been established by Dunn's own disclosure and enormous subsequent scientific literature dealing with nucleic acid probes and nucleic acid hybridization formats, including sandwich hybridization techniques. As particularly disclosed in Kricka's 1988 review article (Exhibit 11), cited *supra*:

> The sandwich hybridization technique described below allows for the large-scale preparation of an activated solid support coated with **probe DNA** (Fig. 8). The **immobilized probe is used to collect the target DNA**, which is **then detected using a labeled second probe** (**which *does not itself interact with the immobilized probe***).
> [bold, underline & italic added]

With respect to **[2]** and **[3]**, Dr. Wetmur respectfully submits in subparagraph 13B(ii), that both assertions by the Examiner are incorrect because Dunn's signaling probe (^{32}P-labeled SV40 DNA) hybridized to the protruding SV40

tail sequences in Dunn's target RNA transcript analyte. Thus, Dunn's signaling probe must have possessed by that very fact a substantial capability for hybridizing to the target RNA transcript analyte. Accordingly, Dr. Wetmur has concluded in his Declaration that Dunn's isotopically labeled signaling probe does not meet the limitation in the pending claims that the signaling entity or entities be substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte.

In subparagraph C (following Paragraph 13), Dr. Wetmur notes that in its July 25, 1997 Amendment, Enzo had argued a distinction on the basis that Dunn's analyte RNA molecule consisted of adenovirus and SV40 sequences in one continuous chain, quoting Dunn and Hassell (1977):

> . . . We have in this way **demonstrated the existence of an RNA molecule consisting of Ad2 and SV40 sequences *in one continuous chain*** and have mapped the location of the sequences which serve as template for its synthesis on the Ad2+ND1 genome. . .
> [Dunn et al., Cell 12:23 (1977); left column, last paragraph; emphasis added]

Following the quote above, in its next statement in its July 25th Amendment, Enzo stated that "the analyte in the present invention could never have in one continuous chain the complementary sequences corresponding to both the molecular bridging entity and the signaling entity for the very clear and simple fact that the latter is substantially incapable of binding to or hybridizing with the analyte."

In that same subparagraph, Dr. Wetmur voices his wholeheated agreement with Enzo's statements regarding the distinction based upon the continuous chain of complementary sequences in Dunn's analyte. In Dunn's case as explained by Dr. Wetmur, the target RNA transcript analyte had adenoviral sequences that hybridized to the immobilized capture probe (adenovirus DNA) and SV40 sequences in its protruding tails that hybridized to the signaling probe (^{32}P-labeled SV40 DNA). According to Dr. Wetmur, the adenovirus and SV40 sequences in Dunn's target RNA transcript analyte lay in one continuous chain, unlike the present invention where such sequences could not so lie in the analyte.

In subparagraph D of his Declaration, Dr. Wetmur declares that based on his review of Dunn and Hassell (1977) and Ranki et al., U.S. Patent No. 4,486,539 (copy attached as Exhibit 19), he has also concluded that as related sandwich

hybridization techniques, both disclosures require the use of two nucleic acid probes having complementary sequences to nonoverlapping sequences in their respective target analytes. The target analyte in both disclosures is further "sandwiched" between their respective sets of two probes, unlike the present invention in which the analyte is not sandwiched between the molecular bridging and signaling entities. In the October 27, 1997 Office Action, the Examiner stated the following:

> Applicants then summarize several references that refer to sandwich hybridization and credit various authors for suggesting or disclosing them. **[1]**It is acknowledged that sandwich hybridization is a phrase that may be applied to both the Ranki et al. type of assay as well as the Dunn et al. type of assay but that the location of the entity that is the target is different but that there are similarities in the sandwiches that are formed. **[2]**Since the Dunn et al. disclosure is directed to mapping RNA sequences this is deemed to be the target. **[3]**This target is located the same both in the Dunn et al. disclosure as well as in the practice of the instant invention and thus supports this rejection. **[4]**It is noted that the target in the Ranki et al. type of sandwich hybridization is in the middle of the sandwich and different from that of Dunn et al. as well as the instant invention.
>
> [bold parenthetical added]

Regarding assertions **[1]** and **[4]**, Dr. Wetmur in subparagraph D(i) points out that the Examiner is correct in his first statement that sandwich hybridization applies to both Dunn and Hassell (1977) and Ranki's U.S. Patent No. 4,486,539. However, as explained by Dr. Wetmur, the assertion that the location of the entity target is different between the two disclosures is incorrect. In both Dunn's and Ranki's disclosures, the target entity is clearly sandwiched between two probes having sequences which are complementary to different and nonoverlapping sequences in the target entity. Dr. Wetmur's reasons with respect to Dunn and Hassell (1977) were already been given in Paragraphs 7-12 of his Declaration. With respect to the Ranki patent attached as Exhibit 21 to his Declaration, Dr. Wetmur points to column 1, line 67, through column 2, line 16; especially column 2, lines 6-16; and also Examples 1-4 and 6, and claim 1.

In subparagraph 13D(ii), Dr. Wetmur points out that regarding **[2]**, the Examiner's assertion is correct that the target in Dunn and Hassell (1977) is the RNA sequences to be mapped, his reasons and conclusions having being given in Paragraphs 8-12 of his Declaration.

Regarding the Examiner's statement in **[3]**, Dr. Wetmur points out in subparagraph 13D(iii) that the assertion that the target analyte in Dunn and Hassell (1977) is located the same as in the present invention is wrong. For reasons given above in Paragraphs 12A and 12B of his Declaration, Dr. Wetmur explains that the analyte in the present invention is altogether different from Dunn and Hassell (1977) both in its location as well as in its relationship to the molecular bridging and signaling entities.

In Paragraph 14, the last paragraph of his Declaration, Dr. Wetmur declares that it is his opinion and conclusion that the present invention and pending claims define elements that are materially different from Dunn and Hassell (1977). In light of the statements and evidence presented in Dr. Wetmur's Declaration, Applicants respectfully submit that the anticipation rejection should be withdrawn upon further consideration.

Apart from Dr. Wetmur's Declaration, Applicants would respectfully point out that if Dunn's signalling probe was intended or designed to hybridize to their capture probe - a necessary element of the present invention - then Dunn and Hassell (1977) would have been detecting their own capture probe - with no regard whatsoever for the target RNA transcript analyte that they were seeking to map. Such a scenario would inevitably have led to a disintegration of the probe-target analyte foundation upon which nucleic acid technology has rested so heavily. In which instance, the terms "target," "analyte" and "probe" would have been synonymously and interchangeably used in the literature. Fortunately, this has not been the case; the scientific world has treated and continues to treat "probe" as an entirely different concept and entity from "target" and "analyte."

Beyond that, Applicants and their attorney can point with confidence to recent pronouncements by the Federal Circuit and its predecessor court on anticipation. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. W. L. Gore & Associates v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983); and Carella v. Starlight Archery, 804 F.2d 135, 138, 231 USPQ 644, 646 (Fed. Cir.), *modified on reh'g*, 1 USPQ2d 1209 (Fed. Cir. 1986); RCA Corp. v. Applied Digital Data Systems, Inc., 730 F.2d 1440, 1444, 221 USPQ 385, 388 (Fed. Cir. 1984). It is not sufficient that the cited reference disclose all the claim elements in isolation. Rather, the cited reference must disclose each element of the claimed invention

"*arranged as in the claim.*" Lindermann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984). Even if the prior art reference includes all the elements that are claimed, if the arrangement of the claimed elements is different from the arrangement of the prior art elements, anticipation will not be found. Further, anticipation will not be present when the prior art reference is lacking or missing a specific feature or the structure of the claimed invention. In interpreting a prior art reference, it is the interpretation of one of ordinary skill in the art that is to be followed.

Under the aforementioned legal principles, it is respectfully submitted that Dunn and Hassell (1970) do not anticipate the present invention because - as described in Dr. Wetmur's Declaration - at least two material claim elements are lacking in the cited reference. These are first, signaling entities that are capable of binding to or hybridizing with one or more molecular bridging entities, and second, signaling entities substantially incapable of binding to or hybridizing with the analyte. Neither element is disclosed in Dunn and Hassell (1977), nor are both elements disclosed in the cited reference as arranged in the present claims.

Before leaving the anticipation issue, Applicants would like to point out that the Examiner's closing statement in the October 27, 1997 Office Action have not been specifically addressed. His remarks concerned Applicants' earlier argument that Dunn et al. did not teach the detection of an unknown analyte. It may well be that Applicants' earlier argument with respect ot Dunn et al. was misunderstood or even unclear. What Applicants had intended to argue was that detecting an unknown target analyte in a sample was different - even to the point of requiring a different mindset - from fishing out messenger transcripts from viral-infected cells. In the former situation, it is not known whether or not the analyte is present in the sample. In the latter situation, the transcripts are known to be present. The Examiner's remarks to the effect that "the analyte must be known regarding sequence in both the Dunn et al. disclosure as well as the instant invention in order to direct the synthesis of the target recognition portion of the bridging entity" are well taken. Aside from this brief mention, further elaboration on this issue is probably not required, particularly because the anticipation rejection is believed to have been overcome by the submission of Dr. Wetmur's Declaration.

In light of Dr. Wetmur's Declaration including 21 exhibits and the foregoing caselaw, it is respectfully submitted that the anticipation rejection by Dunn et al. cannot be reasonably maintained. Applicants respectfully request reconsideration and withdrawal of the anticipation rejection, thereby placing all of the pending claims, 283-362, 364-380, 382-398, 400-404, 406-439 and 441-462, in condition for allowance.

* * * * * * *

SUMMARY AND CONCLUSIONS

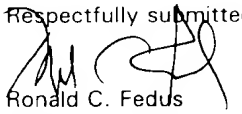
Claims 283-362, 364-380, 382-398, 400-404, 406-439 and 441-463 are presented for further examination on the merits. Claims 300, 315, 321, 328, 347, 364-365, 376, 377, 382-383, 394-395, 400-401, 406-407, 439 and 442 have been amended. In addition, three new claims (461-463) have been added and one claim (440) has been canceled. No new matter has been inserted by any of the foregoing amendments or added claims.

The cost for presenting the claims above is believed to be $594, based upon an additional 27 dependent claims being presented hereinabove. Through amendments of claims 364-365, 382-383, 400-401 and 406-407 and the cancellation of claim 440 altogether, 17 claims were canceled above. By the amendments to claim 439 and the addition of new claims 461-463, 44 additional claims have been presented. Thus, a total of 27 new dependent claims (44 minus 17) have been added above. The fee for 27 additional dependent claims is $594 for a large entity. The fee for presenting multiple dependent claims was previously paid in this application. The Patent and Trademark Office is hereby authorized to charge the amount of $594.00 to Deposit Account No. 05-1135. If any other fee or fees are due in connection with this Amendment or the two-month extension of time request (authorization being given in the extension request), authorization is further hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting the prosecution of this application, the undersigned may be contacted by telephone at 212-583-0100 during the daytime business hours.

Early and favorable action on this application is respectfully sought.

Respectfully submitted



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